Current and Emerging Roles of Whole-Body MRI in Evaluation of Pediatric Cancer Patients

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Jeffrey S. Klein, MD  Hi. I’m Jeff Klein, Editor of RadioGraphics and today I am pleased to have with us Dr. Ravi Gottumukkala, Michael Gee, and Mary Greer from the Departments of Radiology at the Massachusetts General Hospital and the Hospital for Sick Children in Toronto, Canada who are authors of one of our featured papers in the current March 2019 issue of RadioGraphics. Their paper is entitled “Current and Emerging Roles of Whole-Body MRI in the Evaluation of Pediatric Cancer Patients.” Doctors, welcome to our podcast. So Ravi I’m going to begin with you. Your paper reviews the use of whole-body MRI as and imaging tool for children with known cancer and for those who are being screened for cancer predisposition syndromes. The article begins with the review of the technical aspects of performing these studies and in particular the utility of coronal STIR sequences in these examinations. Let’s show Table 1 as you go through the details of the protocol into these examinations.

Ravi V. Gottumukkala, MD  Sure. First off I want to say Dr. Klein thanks so much for having all of us. We’re all very excited to talk about this topic that we think is of importance to the pediatric radiology community. So for whole-body MR examinations I think the big principle is that we’re referring in a most strict sense to imaging from vertex to toes, but that can be modified to be sort of multiple contiguous body regions like the neck, chest, abdomen and pelvis; limiting to that depending on the indications. I think the big overarching theme I want to start with is just by saying that you know I think it’s important to get diagnostically useful information within a reasonable timeframe with this examination because you can really have sequences that end up taking a lot longer if you’re not a little bit judicious with how you select them. So that’s where these sequences come in. So I think it comes down to having two key principles which is the right hardware and also good sequence selection that are sort of high yield for the diagnostic purpose you want. So I’ll quickly just talk about the hardware so I think one principle for this with respect to hardware is to try and minimize time that’s spent basically shifting coils around and moving patients around in between the different sequences and so to the extent that you have hardware like a moving table platform for example and coils that you can position at the beginning of the examination that will allow you to seamlessly transition from one body station to the next, that can be very helpful in minimizing the lag time in between sequences. So that’s a big thing. And I think having dedicated multi-channel coils as well that are surface coils as opposed to using the inbore magna coil can be very helpful in improving your signal to noise ratio and thereby minimizing time and maximizing quality. So that’s sort of the hardware piece. I think with respect to Table 1 the sequence component of things; you know one thing you’ll see if you look at Table 1 is that there are variations in the protocols that are used depending on the institution. We have ours listed on top, but other institutions they have their own set of modified protocols, but the commonalities you see emerge within all of those is that coronal STIR sequence which we find to be reasonably efficient and very valuable in terms of highlighting pathology. So the big benefit of that sequence is it really nicely suppresses all of the background signal from tissues including fat and really highlights lesion conspicuity nicely just because anything pathologic will show up nicely on a STIR sequence particularly osseous lesions in the marrow and so we find that to be a very high yield sequence and we like to do coronal because that allows you to have the minimum number of slices so your through plane slices will dramatically affect your imaging times. If you do coronal across all those stations, that’s sort of the preferred plane. So that’s the STIR sequence, every protocol you see up there has that. And then other sequences that can be useful are basically a single shot fast spin-echo or HASTE depending on which vendor you have. That’s useful because it gives you a lot of bang for your buck in terms of the amount of time it takes to do the sequence which is usually about fifteen to thirty seconds, but also give your reasonably good anatomic detail; can be done either with a breath hold or even free breathing. It’s useful in potentially evaluating in other planes like the axial plane where it complements the coronal that you get with the STIR. It is also good for looking at the bowel potentially just because the GI tract against the abdominal path that’s not suppressed on an axial HASTE is really nice for that. Beyond that, we do like to add in a T1-weighted sequence. That tends to be very good for marrow lesions. You’ll see that in a couple of the protocols on the list as well. So that tends to be useful when you have sclerotic marrow lesions that may not show up well on a coronal STIR sequence. So those are highlighted nicely because you have background fatty marrow signal. And finally you’ll see this in fewer of the protocols, but it’s one of the sort of emerging components of whole-body MRI exams which is a DWI sequence. And now as we’re able to do that faster with techniques like simultaneous multislice imaging. You know it’s more feasible to do that as part of our exam and it adds really a nice functional component in because the rest is sort of anatomic, but this offers the ability to potentially allow functional tissue characterization, you know measurements of ADC values and things like that; and really highlights things like lymph nodes and other lesions very nicely especially when they have high cellularity. So that’s the overarching sort of I think hardware and sequence themes of whole-body MRI.
JSK Terrific. Thank Ravi. So now the paper reviews obviously the strengths and weaknesses of whole-body MR for oncologic indications. Can you detail which body regions in particular are best suited to this examination and then maybe touch on some of the limitations of the technique?

RVG Yeah, absolutely. So I think some of the big principles with respect to regions that it's best for are going to be related to what MRI is best for as we traditionally think about it. For one we always think of MRI as sort of the gold standard modality in the brain; so any sort of pathology or predisposition syndrome where you're looking for brain or things involving the neck where you really need that soft tissue contrast and anatomic detail, MRI is going to be very good for it. So including brain sequences as part of, for example, a patient who has a hereditary paraganglioma sequence to look for things in the neck is very useful. Liver is another area where it tends to excel at, particularly if you add in dedicated liver sequences just because your tissue contrast in the liver is always going to be superior with MR as compared to CT. And then I think where it really excels at as far as staging is in osseous lesions. The benefit there is with that coronal STIR sequence you can really nicely suppress the fatty marrow background and have lesions pop out very nicely. So I think those three areas are where whole-body MRI really shines and those are areas where you know you're often looking for metastases in the liver and bones and it depends on the malignancy you're specifically looking for. So as far as limitations, I think that the two areas that are worth mentioning are we tend to want to look at the lungs when we're staging certain types of cancers and I think at present time whole-body MRI is and MRI techniques in general are not quite at the point where they can supplant CT just because you have that really high spatial resolution on CT looking for these tiny nodules in an organ that doesn't sort of have much intrinsic signal on MR sequences and so when you're looking for lesions that are less than say about six millimeters, it can be challenging to reliably have sensitivity for those with MR sequences. And so for malignancies where we specifically want to stage for lung metastases and where those might impact management, we still routinely will use a dedicated chest CT for that, but relative to other areas of the body where you have to employ CT, the radiation dose is somewhat lower because it's a tissue that penetrates more easily. So lung is one area where I would say we're still working on sequences that can potentially help highlight the conspicuity of small pulmonary nodules. And then the other area is with lymph nodes. I think this is always the classic challenge with CT was well where you know with anatomic imaging where you're going by size criteria as compared to PET. Size criteria can be misleading. It can have prominent lymph nodes that are over a centimeter that are just reactive. You could have sub-centimeter lymph nodes that can be missed on whole-body MRI in some cases, or that you don't necessarily classify as being pathologic, but that are actually involved. So that still I think remains a challenge and DWI to some degree is helping clarify that. I think going forward as we are better able to have DWI sequences where we can measure ADC values in smaller and smaller lesions, that may be something going forward that we can be able to use MRI for is to differentiate in the same size node whether one is potentially malignant based on ADC value versus the other not, but I think at present time you know the anatomic component of nodal imaging is still to some degree a limitation of that.

JSK Sure. That's terrific Ravi. Thanks so much. So Michael let's move on. After you review some contrast agent issues and rapid acquisition techniques including as Ravi mentioned simultaneous multislice imaging and also you touch on sedation issues as well as billing for whole-body MR which is obviously an issue that needs to be addressed. Your paper reviews applications related to pediatric neoplasms beginning with lymphoma. Let's look at Figure 2 if we can I think which nicely illustrates a case of Hodgkin lymphoma.

Michael S. Gee, MD, PhD Sure and again I just want to reiterate that I wanted to thank you and staff from Radiographics for giving us the opportunity to talk about our work. Some of the figures that are in the paper subsequent to the Table 1 are giving specific patient examples of applications of whole-body MRI and how lesions better seen on whole-body MRI compare to their appearance on other imaging modality. So Figure 2 is an example of a 17-year-old patient with Hodgkin lymphoma who had both a PET CT as well as a whole-body MRI resembling closely spaced in time and it gives us an opportunity to compare the different modalities. One of the assumptions underlying the use of whole-body MRI that I think you touched on earlier is the fact that in children who have a high likelihood of having cancer and are likely to need multiple imaging studies over time, the main advantage of whole-body MRI is the lack of ionizing radiation. So this is an example in Figure 2 of a newly diagnosed patient who has cancer. You can see in panels A and B Ravi mentioned the single shots T-2 sequence as well as DWI sequences that are a really important part of whole-body MR. The idea of DWI again is that we're trying to look at the relative motion of water molecules inside of cells and the idea is that patients who have cancer that cancer cells are very densely packed within tumors. We see that restriction in water movement within those cancer cells as a relatively low ADC coefficient or a low ADC value. It's something that reproducible and quantitative and goes beyond the anatomic visualization of tissue and it's similar to what Ravi was saying. In lymphoma patients the current gold standard is PET CT so we use the CAT scan portion of a PET CT which is Figure C, panel C and panel F of that figure to show that both that there are lymph nodes that are enlarged and then we use the FTG PET portion of the PET CT to look at metabolic activity. Again FTG is glucose analog. It's taken up by cancer cells that are highly metabolically accurate. And so in panel D what we're seeing is that those very dark spots within the lymph nodes are showing us that those are lymph nodes that are very densely metabolically active and much more likely to be cancerous. And so comparing panels B and D are showing us that the use of DWI is able to get us similar to the characterization of PET. Obviously by a different mechanism, PET is showing us that these are lymph nodes that are metabolically active and likely cancerous. DWI is showing us that these are lymph nodes that are very densely packed with cells and also likely to be cancerous. So again part of when you're trying to diag-
nose cancers in children at an early stage is that not only do you want to see them anatomically as masses and lesions in the body that aren’t supposed to be there, but in subtle cases where you might not see a very big tumor can you look at that functional information and so this is a nice example showing that the functional information of DWI complements MRI in the same way that PET compliments a PET CT.

JSK Terrific. Well Michael in discussing the use of whole-body MRI in solid malignancies, you focus on the evaluation in particular of small round cell tumors such as a neuroblastoma, Ewing sarcoma. Let’s review Figure 6 which shows the utility of MR in a patient with Ewing sarcoma.

MSG Sure. Again so this is a 13-year-old male who had metastatic Ewing sarcoma and again really highlighting the power of whole-body MRI to diagnose lesions in multiple whole-body locations. As you and Ravi had discussed earlier, there’s certain areas of the body that MRI is naturally very good at looking at. You know areas such as the brain, such as the bony pelvis because there’s a lot of soft tissues, fine soft tissue structures in those areas that need to be distinguished in. The intrinsic soft tissue contrast of MRI is better in those locations than CT which is basically just imaging on the basis of x-ray beam attenuation property so that’s really not getting at sort of more of the soft tissue characterization that we can use with MR. So this is an example of a patient who had a pelvic Ewing sarcoma, had a lesion in the femur which you can see in panel A showing that the corresponding lesion on a CT scan that was performed closely spaced in time, that finding was very subtle on CT and again one of the advantages of MR is bone marrow characterization and so you can see on that STIR image as Ravi was talking about earlier. Not only the cancer cells themselves that have increased water that can be seen on the STIR image, but the fact that many of these aggressive malignancies illicit an inflammatory reaction from surrounding normal bone and that inflammation that surrounds it is something that we see very well on MRI and part of the reason why MRI is often better than CT in subtle bone lesions. Ewing sarcoma as we know is an aggressive bone malignancy as well and so these are tumors that tend to grow very quickly and again induce a very strong inflammatory reaction. The other panel figures were showing some additional metastatic lesions in other parts of the body. I highlight the panel E which is actually a lesion in the lungs. It was an 8mm metastatic pulmonary nodule. The patient had had a CT scan previously that had documented that it was there so it was a lesion that was already known, but the lung is traditionally thought of as an area that MRI is relatively weakened because of the fact that the air in the lungs can affect the magnetic field and cause susceptibility artifacts that make it difficult to see lesions. But showing that in cases where you have good image quality, again patients are also breathing and that respiratory motion in the lungs can also make it difficult to see lesions, but in cases where patients are cooperative and lesions are solid and not ground-glass or not sort of other lesions that are not as solid and not as well seen, MR actually does have very good spatial resolution for seeing small lesions. So that was an example of a small sub centimeter lesion that MR picked up very well.

JSK Terrific. Thanks Michael. Mary let’s move on to talk with you. Mary the latter section of the paper reviews the cancer predisposition syndromes. It looks at the American Association of Cancer Research has a defined role for whole-body MR in screening for selected syndromes. Let’s take a look at Table 2 with provides a summary of their recommendations as they relate to whole-body MRI and perhaps you can focus on those syndromes where you currently employ this technique most often.

Mary-Louise C. Greer, MBBS Absolutely and reiterating from Mike and Ravi thanks again for the kind invitation to participate in the podcast. So the AACR put together a team of different clinicians across the spectrum in pediatrics in the end of 2016 and to really express this issue of surveillance in cancer predisposition syndromes in children. The threshold that was established in terms of working out whether surveillance was warranted or not, was really the determination that if there is a chance of a tumor happening under 20 years of age that’s five percent or more, then some sort of surveillance is justified. The group of people brought together involved people from obviously genetics, pediatric oncology, endocrinology and radiology - my colleagues Lisa States and Stephan Voss also participating in this on the radiology side and from this we’ve distilled after looking at around about fifty different syndromes that there were a handful for whom we could reasonably justify performing whole-body MRI for all the reasons Mike and Ravi have articulated in terms of its increased conspicuity of lesions but really minimizing the risk of adverse effect we hope. One of the challenges obviously being the use of sedation or anesthesia. And certainly the balance in that has determined who we image, when we start, when we stop. The key one that we tend to look at most commonly here at Sick Kids is Li-Fraumeni Syndrome and also the Hereditary Paraganglioma-Pheochromocytoma Syndrome. We have a small number of other syndromes that we image less regularly and the thing that’s important really to remember, these are recommendations. This is not a lot of evidence as yet. This is a starting point drawing on experience from the literature as well as to different clinical groups that already have established some guidelines and we fully expect that these will evolve over time and indeed the AACR is currently is currently in the process of asking us to look at those already in 2019 to see if we can modify those. So in particular Li-Fraumeni Syndrome is one area that is of high value. We’ve done some studies under the guidance of David Malkin and Anita Villani here at Sick Kids looking prospectively at two groups of patients that were streamed into - by patient choice - surveillance and non-surveillance and those patients that elected to have surveillance of which whole-body MRI was a crucial part, together with clinical examination and biochemistry, the 5-year survival was around about ninety percent whereas those patients who elected not to undergo surveillance the 5-year survival was closer to fifty percent. So there’s certain value and in those patients that malignancy was identified, about thirty percent of the studies were solely due to whole-body MRI and when we added dedicated brain MRI to that, the yield was about fifty percent for malignancy. So there’s certainly been shown to be evidence in this patient population with Li-Fraumeni syndrome in whom there’s a
significant lifetime risk of cancer. And in terms of the type of imaging that would be performed for these patients, when they've been diagnosed we carry out whole-body MRI - in this instance we do do vertex to toes or feet in these patients annually. We then do a dedicated brain MRI with contrast the first time around and then unless there's an abnormality shown we'll elect to do it without contrast for ongoing surveillance. And when they reach the point of not needing any sort of sedation or anesthesia, and typically at Sick Kids we would use GA for the most part, and then we'll interchange doing whole-body MRI with a less detailed brain study to doing a more detailed brain study in conjunction with whole-body MRI and alternating between those at six month intervals for their lifetime. But certainly that's been the syndrome that's really been the one that we have shown the most evidence for the utility of whole-body MRI and surveillance screening and ideally to be able to pick up the related tumors - in this patient population that includes different types of brain tumors, adrenocortical carcinomas, osteosarcomas, soft-tissue sarcomas and as we get into the early 20s early onset of breast cancer are the key ones and so it's certainly shown value in those. The other syndromes are less high incidence of malignancy, but certainly with things like Hereditary Paraganglioma and Pheochromocytoma, we certainly do see "pheos" (pheochromocytomas) in those patients. We've shown some examples in our paper of one patient with that, and related malignancies that can be renal tumors for example as well, although of lower incidence.

**JSK** Terrific. And so Mary to follow-up on that can we review Figure 13 which shows the use of a coronal STIR sequence in patients with neurofibromatosis type one?

**MCG** Absolutely. So this patient population is a group that we don't image as obviously as Li-Fraumeni syndrome. We typically suggest for these patients that they just have one whole-body MRI, again vertex to toes, at that point where they transition to adults - from pediatrics to adult care. And so in this example it's a 15-year-old boy who had a coronal STIR – our workhorse sequence - and this is showing that there are a number of plexiform neurofibromas particularly involving the brachial plexus, in the paraspinal region in the cervicothoracic junction as well as in the lumbar region, and in addition to that there are some pelvic tumors there as well. And they have the characteristic appearance of the target sign that we see on T2-weighted sequences of STIR and fat-suppressed T2 and T2 HASTE that we've suggested as alternate sequences. The utility of this in these patients with neurofibromatosis type one is to really to give us an idea of the location, the number and the size of lesions, and over time that forms a baseline looking for evidence of any rapid increase in size. We don't typically do contrast at this point. This is purely for surveillance to determine disease burden and if we have ongoing symptoms of pain or increase in size, then we might elect to do contrast and do some more high resolution targeted imaging through an area of particular clinical concern.

**JSK** Terrific. Well thank you for that. So Ravi, Michael, Mary, I want to thank you for taking time today to discuss your paper on the use of whole-body MRI in the evaluation and screening of pediatric cancer patients. The paper can be found in the current March 2019 issue of *RadioGraphics*. Doctors thanks so much.

Thank you.